**PATENT**
**ATTORNEY DOCKET NO. 28967/35255A**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Ferrell *et al.*

Serial No. 09/375,248

Filed: August 16, 1999

Title: SCREENING AND THERAPY FOR LYMPHATIC DISORDERS INVOLVING THE FLT4 RECEPTOR TYROSINE KINASE (VEGFR-3)

Group Art Unit: 1634

Examiner: Betty J. Forman

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on September 19, 2003

Nabeela R. McMillian
Reg. No. 43,363
Attorney for Applicants

**DECLARATION UNDER 37 C.F.R. § 1.131 OF DR. ROBERT FERRELL IN RESPONSE TO OFFICE ACTION DATED MAY 19, 2003**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Robert Ferrell, do hereby declare and state as follows:

1. I am familiar with the contents of the above-identified U.S. patent application (hereinafter, the "patent application") and with the Office action from the United States Patent and Trademark Office (hereinafter, the "Patent Office") dated May 19, 2003. I have reviewed the amended claims that I understand will be filed for the patent application with this declaration and have attached the claims as Exhibit A. I make this declaration for the following purposes:

a. to provide facts known to me that may be relevant to the issue of inventorship in the present application;

b. to provide facts relating to the publication date of Kimak *et al.* (*American Journal of Human Genetics, 63(4)*, Abstract 180, A185 (1998); hereafter "Kimak *et al.*"); and

c. to provide facts relating to Witte *et al.*, (*Lymphology*, 31:145-155, (1998); hereafter "Witte *et al.*"), which facts may be pertinent to the Patent Office's rejections under 35 U.S.C. §102(a) of claims 1-2, 4-10, 37-40, and 42-47.

2. I am a named co-inventor of the subject matter of one or more claims in the patent application, as well as a named co-author of Kimak *et al.* Kimak *et al.* was co-authored by Mark A. Kimak, Elizabeth C. Lawrence, Kara L. Levinson, M. Michael Barmada, Judith H. Esman, David N. Finegold and me, and was published in October 1998. I am familiar with the contributions made by all of the co-authors of Kimak *et al.* to the subject matter reported in that document. By virtue of communications with Kari Alitalo and Marika Karkkainen as part of a research collaboration between our laboratory in the United States and their laboratory in Finland, I am also familiar with the contributions made by Kari Alitalo and Marika Karkkainen to the subject matter of the patent application.

3. Kimak *et al.* is an abstract that summarizes and analyzes linkage and mutation in VEGF-C receptor gene in hereditary lymphedema. In doing so, Kimak *et al.* describes phenotyping of multigenerational families for autosomal markers to identify *Flt4* as a likely putative candidate gene for lymphedema. The abstract further discusses sequencing of *Flt4* exons in such families to identify mutations as a plausible candidates predisposing family members to familial lymphedema. The work summarized in this abstract was performed largely by the team of co-authors listed on the article. However, David Finegold and I are the individuals that conceived the project and how to perform it, and interpreted the data. The contributions of the other co-authors reflect work performed under the direction and control of David Finegold and I. The other coauthors of Kimak *et al.* (*i.e.*, Mark A. Kimak, Elizabeth C. Lawrence, Kara L. Levinson, M. Michael Barmada, and Judith H. Esman), were not listed as co-inventors of the application because their contributions were made under the direct supervision and direction of David Finegold or me.

4. The Kimak *et al.* abstract provides some evidence that mutations in Flt4 may be plausible links with hereditary lymphedema. Our laboratory collaborated with Kari Alitalo and Marika Karkkainen in Finland, who conducted the functional analysis (*e.g.*, Flt4 signaling studies) reported in the patent application but not reported in Kimak *et al.*

Through the work of Kari Alitalo and Marika Karkkainen, for example, the collaboration discovered that Flt4 mutations reduce ligand-mediated signaling relative to the wild type Flt4/VEGFR-3 polypeptide. Kari Alitalo and Marika Karkkainen made other contributions to the project and the patent application as well.

5. Witte *et al.* was published in the December 1998 issue of the Journal *Lymphedema.* As a rationale for performing their studies, the authors of Witte *et al.* state "[b]ased on the report of Kimak et al (12) of linkage markers at 5q34-q35, we examined data from our genome-wide search." (See Witte *et al.*, page 147, second column, beginning of second paragraph). Reviewing the reference listing of Witte *et al.*, I note that the "Kimak et al (12)" reference being referred to by Witte *et al.*, is our work described in the Kimak *et al.* abstract discussed above, and published in October of 1998.

6. The only discussion of mutations in the VEGF-C receptor and correlation of such mutations with hereditary lymphedema in the Witte *et al.* reference are found with respect to the discussion in Witte *et al.* of the data reported in Kimak *et al.* Therefore, Witte *et al.* does not contain any disclosure relevant to the correlation of hereditary lymphedema with VEGFC-receptor mutations other than those disclosed by us in Kimak *et al.*

7. The above outline shows that Kimak *et al.*, was published in October of 1998 and Witte *et al.* was not published until December of 1998, and shows that David Finegold and I were in possession of the subject matter of the claimed invention prior to the effective date of the Witte *et al.* reference.

8. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Date Sept. 17, 2003

Dr. Robert E. Ferrell

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a. to provide facts known to me that may be relevant to the issue of inventorship in the present application;

b. to provide facts relating to Lawrence *et al.* (*American Journal of Human Genetics, 63(4)*, Abstract 1053, A185 (1998); hereafter "Lawrence *et al.*", which facts may be pertinent to the Patent Office's rejections under 35 U.S.C. §102(a) of claims 1-2, 4-10, 37-40, and 42-47; and

may be pertinent to the Patent Office's rejections under 35 U.S.C. §102(a) of claims 1-2, 4-10, 37-40, and 42-47; and

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2. I am a named co-inventor of the subject matter of one or more claims in the patent application, as well as a named co-author of both Lawrence *et al.* and Kimak *et al.*

3. Lawrence *et al.* was co-authored by Elizabeth C. Lawrence, Mark A. Kimak, David. N. Finegold and me and has a listed publication date of October 1998. I am familiar with the contributions made by all of the co-authors of Lawrence *et al.* to the subject matter reported in that abstract. Kimak *et al.* was co-authored by Mark A. Kimak, Elizabeth C. Lawrence, Kara L. Levinson, M. Michael Barmada, Judith H. Esman, David N. Finegold and me, and has a reported publication date of October 1998. I am familiar with the contributions made by all of the co-authors of Kimak *et al.* to the subject matter reported in that document. By virtue of communications with Kari Alitalo and Marika Karkkainen as part of a research collaboration between our laboratory in the United States and their laboratory in Finland, I am also familiar with the contributions made by Kari Alitalo and Marika Karkkainen to the subject matter of the patent application.

4. Lawrence *et al.* is an abstract that summarizes and analyzes the genomic organization, sequence, and variation of Vascular Endothelial Growth Factor-C receptor (also referred to as FLT-4). In doing so, Lawrence *et al.* states that "to better understand the structure and variation in FLT4, we examined the genomic sequence in normal individuals by direct sequencing of exons and flanking introns." Comparisons were performed with mouse *Flt1* sequences and certain polymorphisms were identified. It was concluded that the genomic organization shows structural but not sequence homology to mouse *Flt1*, and that the structure of human *Flt4* is highly variable and that the polymorphic variation will be useful for linkage and halotyping analyses. The work summarized in this abstract was performed largely by the team of co-authors listed on the article. However, David Finegold and I are the individuals that

conceived the project and how to perform it, and interpreted the data. The contributions of the other co-authors reflect work performed under the direction and control of David Finegold and I. The other co-authors of Lawrence *et al.* (*i.e.*, Elizabeth C. Lawrence and Mark A. Kimak), were not listed as co-inventors of the application because their contributions were made under the direction and supervision of David Finegold or me.

5. Kimak *et al.* is an abstract that summarizes and analyzes linkage and mutation in VEGF-C receptor gene in hereditary lymphedema. In doing so, Kimak *et al.* describes phenotyping of multigenerational families for autosomal markers to identify *Flt4* as a likely putative candidate gene for lymphedema. The abstract further discusses sequencing of *Flt4* exons in such families to identify mutations as a plausible candidates predisposing family members to familial lymphedema. The work summarized in this abstract was performed largely by the team of co-authors listed on the article. However, David Finegold and I are the individuals that conceived the project and how to perform it, and interpreted the data. The contributions of the other co-authors reflect work performed under the direction and control of David Finegold and I. The other coauthors of Kimak *et al.* (*i.e.*, Mark A. Kimak, Elizabeth C. Lawrence, Kara L. Levinson, M. Michael Barmada, and Judith H. Esman), were not listed as co-inventors of the application because their contributions were made under the direction and supervision of David Finegold or me.

6. As noted in the Lawrence *et al.* abstract, we identified *Flt4* as both a positional and biologically plausible candidate gene for hereditary lymphedema. The Kimak *et al.* abstract provides some additional evidence of mutations in this gene may be plausible links with hereditary lymphedema. Our laboratory collaborated with Kari Alitalo and Marika Karkkainen in Finland, who conducted the functional analysis (*e.g.*, Flt4 signaling studies) reported in the patent application but not reported in either Lawrence *et al* or Kimak *et al.* Through the work of Kari Alitalo and Marika Karkkainen, for example, the collaboration discovered that FLT4 mutations reduce ligand-mediated signaling relative to the wild type

FLT4/VEGFR-3 polypeptide. Kari Alitalo and Marika Karkkainen made other contributions to the project and the patent application as well.

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Dr. Robert Ferrell